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REVIEW

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T cell mediated neuroprotection is a physiological response to central nervous system insults

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Abstract The physiological conditions under which beneficial autoimmunity is evoked have never been documented. We recently demonstrated that autoimmune T cells directed against myelin-associated self-proteins, when passively transferred into rats or mice, reduce the spread of damage after traumatic injury to central nervous system axons. This finding raised a fundamental question: does this beneficial effect represent a physiological neuroprotective response that normally is too weak to be effective and requires boosting, or is it simply the welcome result of an ex vivo manipulation? It appears from our studies that trauma, at least in the central nervous system, evokes a stress signal that activates a T cell dependent response directed against self antigens, and that this response is physiological in nature, beneficial in intent, and amenable to boosting by active or passive immunization.

Keywords Beneficial autoimmunity · Central nervous system trauma · Neuroprotection

Abbreviations *MBP:* Myelin basic protein

An adaptive immune response, evoked by passive or active immunization, can benefit the injured central nervous system

Traumatic insult to the central nervous system causes degeneration of the directly injured neurons and usually also of neighboring neurons that escaped the primary injury but are affected by the toxicity of an extracellular environment rendered hostile as a consequence of the insult [1, 2, 3, 4, 5, 6, 7, 8]. Accumulated evidence from our laboratory shows that the traumatized CNS can benefit from active or passive immunization with myelin-associated antigens [9, 10, 11, 12, 13, 14]. Thus, for example, in the severely injured optic nerve of the rat a significantly smaller number of initially spared neurons succumb to secondary degeneration if they are treated at the time of injury with T cells directed against myelin basic protein (MBP) than in untreated injured controls [9]. We have further shown that the effect of T cell treatment is long-lasting and is manifested both morphologically and functionally [11, 12]. More recently we have found that a similar effect, manifested in improved recovery of hind limb motor activity, is obtained by passive transfer of anti-MBP T cells into adult rats after contusive injury of the spinal cord, provided that the autoimmune T cell treatment is applied not later than 1 week after contusion [14]. Interestingly, although these injected T cells are capable of inducing the paralyzing disease experimental autoimmune encephalomyelitis, they do not interfere with the protective effect of the T cells or the favorable outcome of the spinal cord injury; at most, if administered 1 week after injury, they mask any early signs of apparent recovery and thus delay their onset [14]. The maximal recovery in rats treated with autoimmune T cells 1 week after contusion is similar to that seen in rats that had been treated immediately after the injury. A neuroprotective effect of the autoimmune T cells is also obtained by active immunization (vaccination) of the rats, before or immediately after the injury, with MBP emulsified in incomplete Freund's adjuvant [14]. Passive transfer of anti-MBP antibodies does not result in improved recovery, suggesting that the neuroprotective effect obtained by active immunization with MBP is mediated by T cells (E. Yoles et al., submitted). The protective autoimmunity was not necessarily accompanied by the development of autoimmune disease, as T cells directed against nonencephalitogenic cryptic epitopes of MBP show a similar beneficial effect [9].

This achievement of immune neuroprotection, whether by active or passive immunization, left some key questions unresolved: (a) Does immune neuroprotection represent a purely exogenous manipulation or does it reinforce a physiological response which in its spontaneous

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form is too weak to be effective? (b) Is it possible to achieve the same neuroprotective effect using a safe (i.e., nonpathogenic) antigen? (c) What evokes the neuroprotective response to the T cells, and how is it mediated? These questions are addressed below.

Beneficial aut immunity is a physiological response

We have recently shown that traumatic injury to the rat spinal cord awakens a systemic neuroprotective response that mediates enhanced neuroprotection against subsequent injury to a second CNS site (E. Yoles et al., submitted). This beneficial effect is optimal when the time interval between the two lesions is 7–17 days. In addition, we have demonstrated a neuroprotective effect in newly injured rats injected with splenocytes obtained from the spinally injured rats. This latter finding strongly suggests (a) that protective autoimmunity is physiological, (b) that it is evoked by injury, and (c) that it is transferable by lymphocytes. It thus seems that traumatic CNS injury can evoke a beneficial endogenous autoimmunity, and not only a destructive endogenous autoimmunity, as has been claimed [15].

The concept that an injury-evoked neuroprotective response is mediated by T cells is further supported by our observation that the survival rate of retinal ganglion cells after optic nerve injury is significantly greater in transgenic mice overexpressing a T-cell receptor for MBP than in matched wild-type controls, but is less in transgenic mice overexpressing T cells to the non-self antigen ovalbumin (E. Yoles et al., submitted). It is also important to note that although activated anti-MBP T cells are known to cause experimental autoimmune encephalomyelitis, no disease develops in the transgenic mice used in this study. It is thus possible that while regulatory T cells in the transgenic mice suppress the destructive autoimmunity, they do not prevent expression of the protective autoimmunity. We further suggest that the neuroprotective and the destructive effects mediated by autoimmune T cells are regulated by a common mechanism (J. Kipnis et al., submitted). Moreover, using nude (athymic) mice, we recently found that the outcome of neuronal insult is worse in these mice than in matched wild-type controls (H. Schori et al., submitted), thus further supporting the notion that the endogenous neuroprotection evoked by CNS insult is T cell dependent.

Injury in the CNS is a stress signal that evokes an anti-self response

The concept that autoimmunity, once established, might be harmless or even useful, is not new [16, 17, 18, 19, 20, 21]. However, none of the theories put forward in this connection has described a situation in which the body calls for help from an autoimmune response. Even the danger signal model, which basically argues against discrimination between self and non-self in characterizing the signals triggering a beneficial immune response, views the response to self as a by-product of an adaptive immune response, a side effect that soon decays in the absence of a second signal to maintain it [16]. We suggest, on the basis of our results, that the autoimmune immune activity evoked in response to CNS trauma (E. Yoles et al., submitted; J. Kipnis et al., submitted; J. Schori et al., submitted) is a purposeful physiological event.

The adaptive immune response has generally been considered as an immune activity evoked by the organism to cope with stressful conditions caused by pathogens. Our observations suggest, however, that a stress signal transmitted from a traumatized tissue (in this case the CNS) to the immune system need not be pathogen related. This would imply that a response to self is not a quirk of nature, or an aberrant immune response, but rather a physiologically purposeful event.

Immunologists have traditionally viewed the functions of the adaptive immune response as neutralizing pathogens, preventing pathogen invasion of tissue, or counteracting the damage caused by pathogens that manage to invade. The damage caused by trauma, however, does not involve pathogens and thus has not been regarded by immunologists as posing the type of danger to the tissue that necessitates an adaptive immune response. Opinions differ as to the mechanisms by which self becomes invisible to the immune system, for example, by clonal deletion, anergy, or tolerance [16, 17, 18, 19, 20, 21]. If trauma can indeed act as a stress signal that activates a helpful immune response, a number of questions arise. Does this occur in all tissues? If not, why not? Since the role of the immune system is tissue protection, defense, and maintenance, does this signal always operate for the organism's benefit? How is it related to autoimmune disease? Does the trauma-related stress signal vary from tissue to tissue? It is possible that what determines whether a beneficial autoimmune response is evoked in a particular tissue depends on the severity of the threat. Trauma in the CNS potentially poses more of a threat to the individual than trauma in other tissues because of the self-perpetuating spread of degeneration [1, 2, 3, 4, 5, 6, 7, 8, 22] and the fact that terminally damaged neurons are irreplaceable. The stress signal elicited by trauma in the CNS can therefore be expected to be more profound. For example, the traumatized CNS might transmit – in addition to the signal sent by the damage itself – a second, as yet unidentified, distress signal, thereby converting T cells into effector helper cells with trauma-related activity. This implies that in traumatically injured non-CNS tissues that do not evoke an autoimmune response (beneficial or otherwise) the second signal is insufficient to activate T cells and/or to maintain them in an active form that enables them to become effectors. The specificity of the evoked T cells (in terms of the self-epitopes that activate them and are recognized by them) might, even in the CNS, vary according to the site of injury. It is conceivable that trauma-related distress signals activate T cells of other relevant

self-epitopes for protective purposes. It is also possible that in some individuals, because of their genetic make-up, an injury-induced beneficial autoimmune response cannot be expressed (J. Kipnis et al., submitted).

How does the response evoked in the protective autoimmune T cells exert its effect on the damaged tissue? It is possible that the active molecules produced by the effector helper T cells after trauma-associated damage are neurotropins [12, 23, 24]. It also seems reasonable to assume that their secretion by the effector (autoimmune) T cells is antigen dependent [12]. An alternative possibility is that the T cells involved in autoimmune protection acquire a novel phenotype, which we have tentatively designated Th-NP, i.e., helper T cells with a propensity for neuroprotection (O. Butovsky et al., submitted).

Active immunization for neuroprotection with a safe peptide

If the observed immunological neuroprotection is to be exploited for clinical purposes, it will obviously be necessary to find ways immunize with "safe" CNS antigens, or with antigens that cross-react with self antigens but are themselves nonpathogenic. We have found that active immunization of rats or mice with a nonpathogenic cryptic epitope derived from myelin oligodendrocyte glycoprotein, a myelin protein, is as effective as MBP in protecting damaged optic axons by slowing down the death of their cell bodies [25]. Because individuals differ in their repertoires of MHC class II antigens, however, it is not possible to define a universally "safe" sequence in potentially pathogenic myelin-associated proteins for clinical use.

In exploring ways to achieve neuroprotection by vaccination we have examined the therapeutic efficacy of a synthetic polymer, copolymer-1, which can cross-react with T cells specific to myelin proteins, and is in clinical use as a drug for patients with multiple sclerosis [26]. Thus, its safety in terms of pathogenicity has already been established. To our surprise and satisfaction, active immunization with this drug, or passive transfer of the autoimmune T cells with which it cross-reacts, led to significant neuroprotection, manifested by significant reduction in secondary degeneration, after optic nerve injury in rats or mice [27].

Implications

Taken together, the results of our studies further imply that autoimmune protection, being the body's own physiological (although inadequate) response to injury, is worth augmenting for therapeutic purposes [28, 29]. Such a therapeutic approach, which until now has been neglected and even shunned by immunologists, might represent a therapeutic gold mine. Its exploration can also be expected to unravel some long-standing enigmas, including the meaning of a danger signal in immunology and the way in which the immune response is evoked. It is clear from our studies that the question is not whether autoimmunity is produced, or how self is distinguished from non-self, but how to control the immune response to self so as to derive the maximum benefit with minimum threat.

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